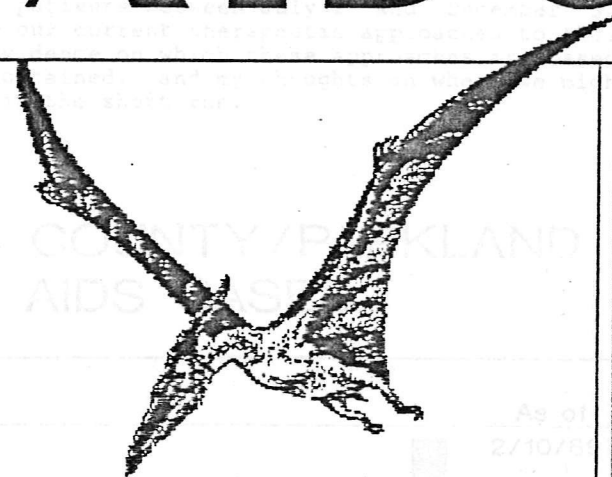
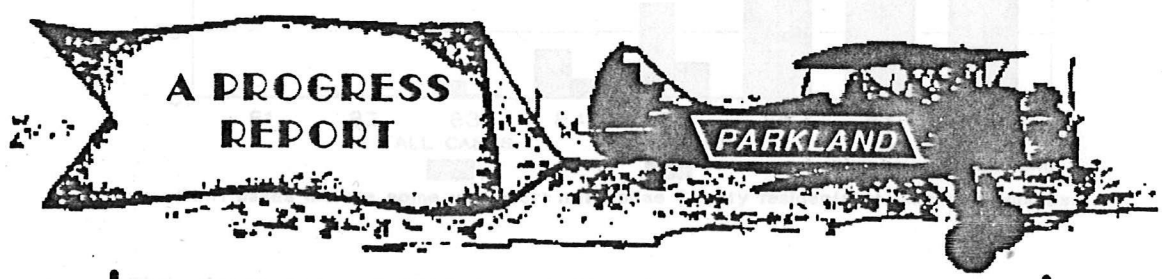
AIDS



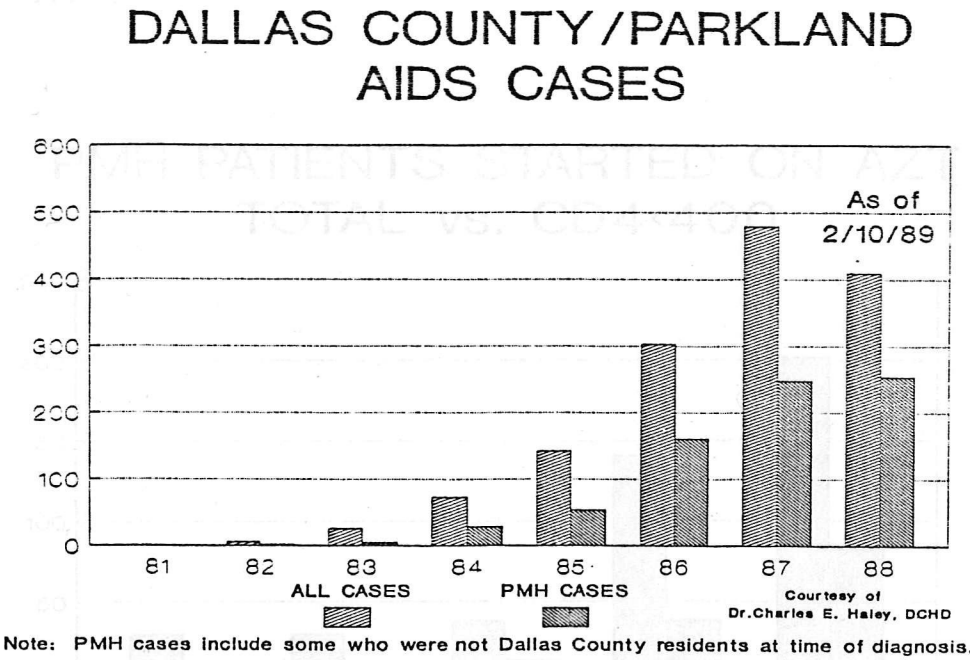
A PROGRESS REPORT



By December 31, 1988, 752 patients with AIDS had received some or all of their care at Parkland Memorial Hospital. The purpose of this discussion is to review our experience with these patients.

The first part of this discussion will describe the course of the AIDS epidemic at Parkland, and discuss what influence AZT and aerosolized pentamidine may have had on it. Our experience with AZT and aerosolized pentamidine will be presented, and compared to what others have reported. The second part will review our experience with the complications of HIV infection that were fatal in any of our patients between July 1 and December 31, 1988. I will outline our current therapeutic approaches to these complications, the evidence on which these approaches are based, the results we have obtained, and my thoughts on where we might be able to do better in the short run.

Figure 1



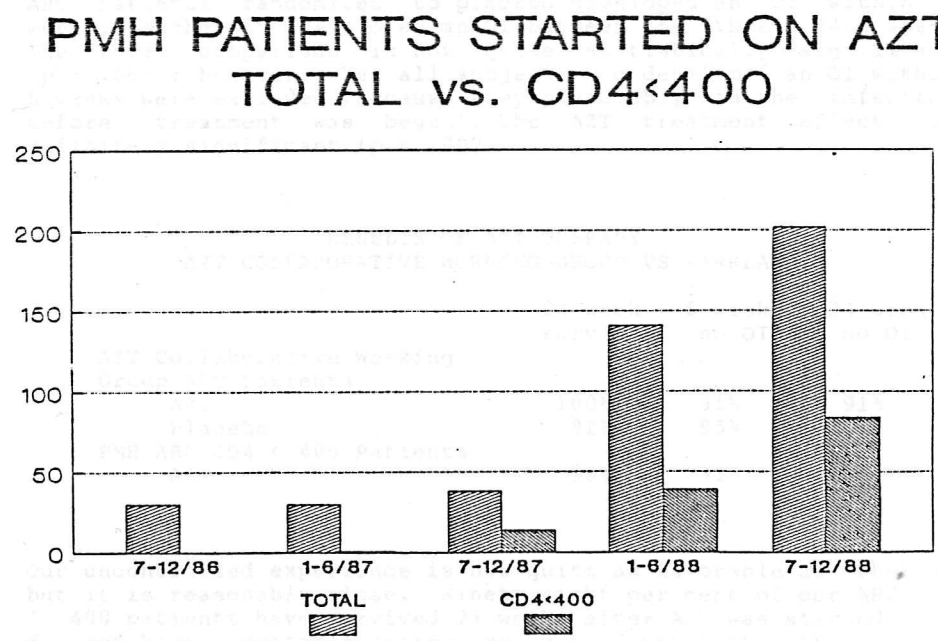
Note: PMH cases include some who were not Dallas County residents at time of diagnosis.

The first case of AIDS in a Dallas County resident was diagnosed in 1981. From then through 1987, the AIDS epidemic grew in Dallas County at roughly the same rate it grew throughout the United States. In 1988, however, the growth of the epidemic in Dallas County residents may have abated somewhat. The Dallas County

Health Department reported 479 new AIDS cases diagnosed in its residents during 1987; but by February 6, 1989 the Dallas County Health Department had recorded only 412 new AIDS cases for all of 1988. The projected total for 1988 was 680 new AIDS cases.

Because of reporting delays, the Dallas County figures for 1988 will not be complete until the summer. Parkland's own figures, however, are not subject to most of these delays, so our 1988 totals are virtually complete. The registry we maintain in the AIDS Clinic recorded 247 new AIDS cases in Parkland patients in 1987, and it had recorded 253 new AIDS cases in Parkland patients in 1988 by December 31, 1988. By February 6, 1989 we had added only 3 more cases to our 1988 total. Whatever the Dallas County Health Department's final numbers prove to be, it now appears that the final number of new AIDS cases at Parkland in 1988 will be only slightly ahead of the number of new AIDS cases at Parkland in 1987.

Figure 2



One possible explanation for Parkland's apparent reprieve is that AZT and/or aerosolized pentamidine treatments have delayed the onset of AIDS in our patients, and this is why we diagnosed fewer AIDS cases in 1988 than we expected. This figure shows the number of Parkland patients, at 6 month intervals, that were started on AZT. The figure also shows the number of these patients, in each interval, that were started on AZT before they had met the CDC criteria for AIDS. By December 31, 1988, 453 of Parkland's patients had been treated with AZT; 138 of them have been started on AZT before they met the CDC criteria for AIDS. All 138 patients either had ARC or a CD4 lymphocyte count < 400.

The AZT Collaborative Working Group (1) found that 100% of their ARC patients randomized to AZT survived 24 weeks, compared to 81% of their ARC patients randomized to placebo ($p < .016$). When the subjects were stratified by CD4 lymphocyte count, 100% of those with a CD4 count of 101-499 randomized to AZT survived 24 weeks, compared to 91% of those with a CD4 count of 101-499 randomized to placebo ($p < .028$). Comparable results were obtained when development of an opportunistic infection, rather than death, was used as the endpoint. Nine percent of their ARC patients randomized to AZT developed an opportunistic infection within 6 weeks, but none developed an opportunistic infection (OI) between the 7th and the 24th week; in contrast, while only 5% of their ARC patients randomized to placebo developed an OI within 6 weeks, another 25% developed an OI between the 7th and 24th week. The total comparison is not quite statistically significant ($p = .066$); however, when all subjects who developed an OI within 6 weeks were excluded (because they presumably had the infection before treatment was begun), the AZT treatment effect is definitely significant ($p < .002$).

RESULTS OF AZT THERAPY
AZT COLLABORATIVE WORKING GROUP VS PARKLAND

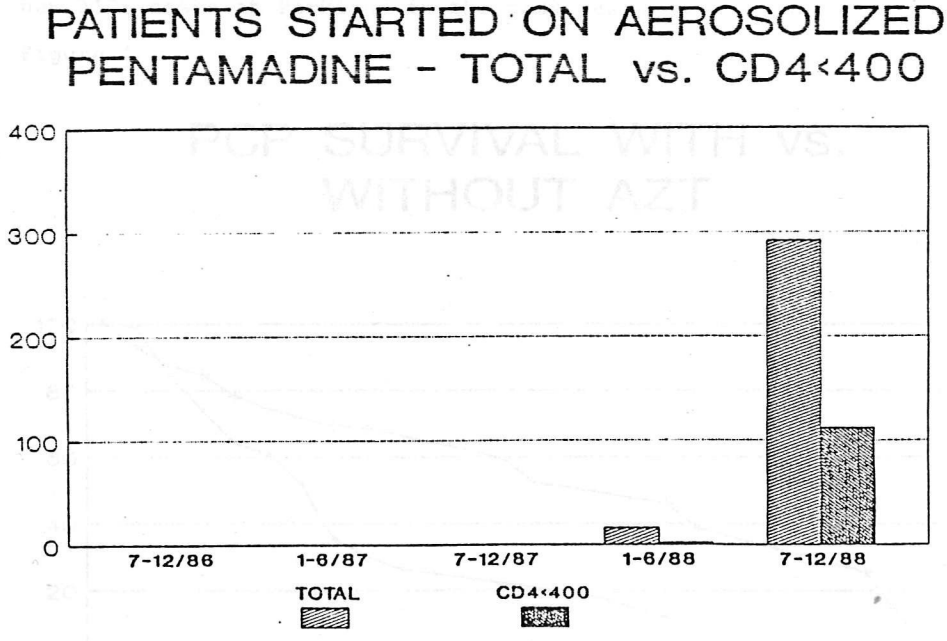
	24 week survival	6 week no OI	24 week no OI
AZT Collaborative Working Group ARC Patients			
AZT	100%	91%	91%
Placebo	81%	95%	70%
PMH ARC/CD4 < 400 Patients			
AZT	98%	92%	84%

Our uncontrolled experience is not quite as favorable as theirs, but it is reasonably close. Ninety-eight per cent of our ARC/CD4 < 400 patients have survived 24 weeks after AZT was started. We do not have a suitable control group to demonstrate that these patients were as sick as the AZT Collaborative Working Group's patients, but the rate at which our treated patients developed opportunistic infections suggests that they were. Eight per cent

of our patients developed an opportunistic infection within 6 weeks of beginning AZT, compared to 9% of the AZT Collaborative Working Group's ARC patients. While none of the AZT Collaborative Working Group's ARC patients developed an opportunistic infection between the 7th and the 24th week, an additional 8% of ours did.

These data suggest that AZT was as effective at prolonging life in our pre-AIDS patients as it was the the AZT Collaborative Working Group's patients, although it may have been somewhat less effective at preventing opportunistic infections. We feel these data justify our continued use of the AZT Collaborative Working Group's experience as the basis of our own practice, which is to recommend that our patients begin AZT when they develop ARC or a CD4 lymphocyte count < 400. However, these data not explain the apparent abatement of new AIDS cases at Parkland in the past year.

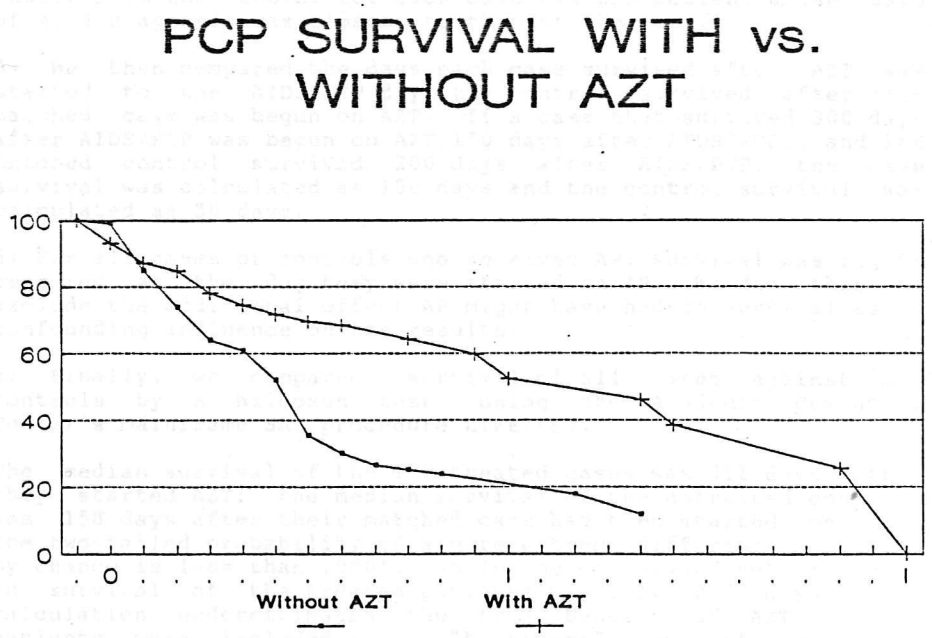
Figure 3



The other treatment that might possibly explain the abatement in new AIDS cases is aerosolized pentamidine (AP) (2). This figure shows the number of Parkland patients, at the same 6 month intervals, that were started on AP. The figure also shows the number of these patients, in each interval, that were started on AP before they met the CDC criteria for AIDS. During the past year Parkland treated 308 patients with AP; 99 of them have been started on AP before they met the CDC criteria for AIDS. As with AZT, the 99 patients we started on AP before the diagnosis of AIDS either had ARC or a CD4 lymphocyte count < 400.

By December 31, 1988, at a mean follow-up of 120 days, only one of these patients had developed pneumocystis pneumonia (PCP). Lacking randomized controls, I cannot prove these patients were as sick as our AZT patients, but they met the same criteria (ARC or CD4 < 400) as the AZT patients, and almost all of them were on AZT as well as AP. However, even if AP is as effective as it appears to have been, AP was only started at Parkland in June 1988, and the apparent abatement of new AIDS cases at Parkland had begun well before this time. For the present, the best we can say is that AZT and AP appear to have been effective therapies for patients with ARC and a CD4 count < 400, but their institution does not completely explain the apparent abatement of new AIDS cases at Parkland in the past year.

Figure 4



We have somewhat better data to show that AZT and AP have prolonged our patients' lives after they have developed AIDS. Once again, we have given AZT and AP in open, uncontrolled trials rather than in randomized, placebo-controlled ones. However, our selection of patients for AZT and AP has been unbiased; as these treatments became available to us, we have offered them to all patients who had a CD4 lymphocyte count consistently less than 400. Because our selection was unbiased, we feel we can appropriately compare the outcomes of our patients who received AZT and/or AP with the outcomes of those who did not using the retrospective case-control method (3).

The methodology for the AZT comparison was as follows:

1) We limited our analysis to patients who had met the CDC criteria for AIDS, and who had pneumocystis pneumonia (PCP) on the day the AIDS diagnosis was established.

2) For each of the 172 resulting cases that were started on AZT, we identified the day after AIDS/PCP the patient was started on AZT. If the case had been on AZT before AIDS/PCP occurred, the case was considered to have started AZT on day 0.

3) To identify a control for each case, we identified from the 149 patients that were not started on AZT all those who had survived at least as many days after AIDS diagnosis as that case had survived before that case was started on AZT. The control chosen from the subset for each case was the patient whose date of AIDS diagnosis was closest to that of the case.

4). We then compared the days each case survived after AZT was started to the AIDS/PCP days the control survived after its matched case was begun on AZT. If a case that survived 300 days after AIDS/PCP was begun on AZT 150 days after AIDS/PCP, and its matched control survived 200 days after AIDS/PCP, the case survival was calculated as 150 days and the control survival was calculated as 50 days.

5) For all cases or controls who received AP, survival was right-censored at the day they were started on AP. We did this to exclude the additional effect AP might have had on survival as a confounding influence on the results.

6) Finally, we compared survival of all cases against all controls by a Wilcoxon test, using the Academic Computing Center's mainframe SAS procedure LIFETEST.

The median survival of the 172 treated cases was 411 days after they started AZT; the median survival of the untreated controls was 158 days after their matched case had been started on AZT. The two-tailed probability of a more extreme difference occurring by chance is less than .0001. While the calculated net increment in survival of the treated patients was only 253 days, this calculation underestimates the true benefit of AZT because patients were included in the "treatment" group if they were

given a single prescription for AZT and returned for at least one follow-up visit. "Treated" cases therefore include those who could not tolerate the drug and those who did not take it.

Our experience with AZT in AIDS patients appears quite comparable to that of the AZT Collaborative Working Group (1). In their study, survival at 24 weeks was 96% for AIDS patients receiving AZT and 76% for AIDS patients receiving placebo ($p<.001$); in ours, survival at 24 weeks was 70% at 24 weeks for AZT cases and 35% for non-AZT controls. Similarly, Creagh-Kirk et al. (4) found that, in 4805 patients given AZT under the Burroughs-Wellcome Treatment IND, survival was 73% at 44 weeks after AZT was begun; our corresponding survival was 63%. Since we included all patients who received AZT for at least 2 weeks in our treatment group, since we right-censored all treated patients on the day they began AP, and since about 1/3 of our patients had had PCP more than 120 days before they started AZT (compared to none of the Collaborative Working Group's patients), our analyses are more conservative than those in references 1 and 4; so we do not think our overall experience with AZT has been less favorable that that reported in the literature.

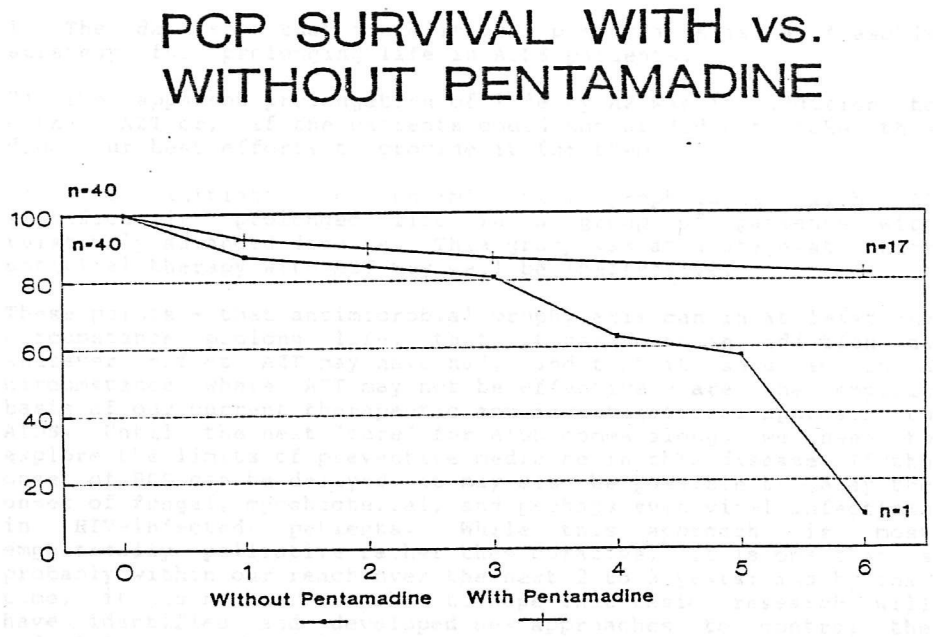
Figure 5

Days After PCP AZT Begun	n	Case Survival	Control Survival	p (Wilcoxon)
0 - 90	88	508	172	<.03
91 - 180	37	681	157	<.02
181 - 270	17	411	59	<.001
271 - 365	13	189	195	NS
>365	17	210	123	NS
All Cases	172	411	158	<.0001

Because so many of our patients were started on AZT more than 120 days after AIDS/PCP, we analyzed the benefit of AZT therapy in our patients as a function of how long after the diagnosis of AIDS/PCP the patient was started on AZT. We found that patients who started AZT within 270 days of AIDS/PCP received a statistically significant benefit from this drug, while those who started AZT after this time did not. Creigh-Kirk et al. (4) have reported a similar observation. Why this occurred cannot be deduced directly from the data, but at least 2 possibilities come to mind. First, the time after AIDS/PCP is a rough proxy for the state of the patient's immune system, which deteriorates over

time. AZT may require, directly or indirectly, a more competent immune system than these late AIDS patients posessed if it is to produce a beneficial effect on survival. Second, patients do not seem to tolerate AZT as well late in the course of their disease as they do earlier in its course (5). The lack of AZT effect in the subsets who were started on AZT later may simply reflect their inability to take the drug. Whatever the reason, our experience is that AZT is less effective when it is started late in the course of AIDS.

Figure 6



Our initial experience with AP has been very encouraging. Of our 308 patients who have received AP, 40 had had PCP at the time of AIDS diagnosis, received AZT, and survived at least 365 days after AIDS diagnosis before receiving AP. We used the retrospective case-control method described above to compare survival of these 40 cases to survival of 41 controls who had had PCP at the time of AIDS diagnosis, received AZT, survived at least 365 days after AIDS diagnosis, but had not received AP. Potential controls were all controls that had survived as many days as the case had survived before the case was begun on AP; the control chosen was the one whose AIDS diagnosis date was

closest to that of the case. Case survival was calculated from the day the case was begun on AP; control survival was calculated from the day its matched case was begun on AP.

Survival of the treated cases was 87% at 90 days and 82% at 180 days, and there were 17/40 cases known to have survived at least 180 days after AP was begun. Survival of untreated controls was 82% at 90 days and 10% at 180 days, and there was only one control known to have survived at least 180 days after its matched case was begun on treatment. The two-tailed probability of a more extreme difference occurring by chance is <.025.

Three points can be made about these data:

1) The data show that antimicrobial prophylaxis is a feasable strategy for prolonging life in AIDS patients.

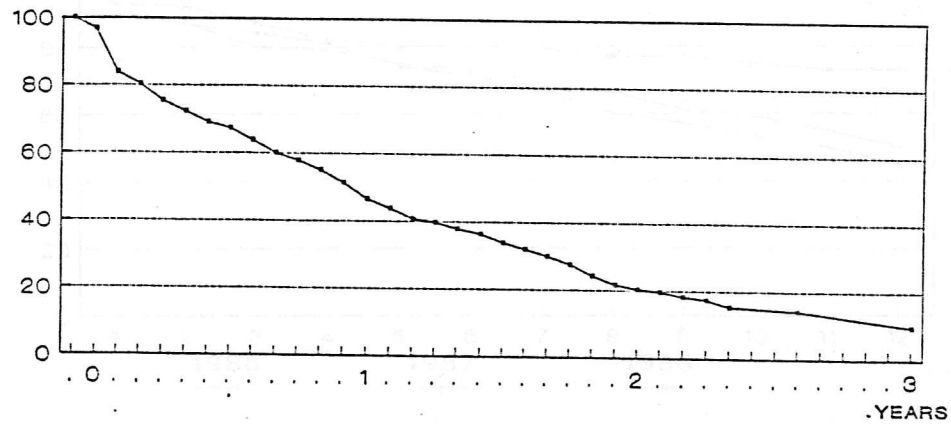
2) The apparent prolongation of life by AP was in addition to either AZT or, if the patients could not or did not take this drug, our best efforts to provide it for them.

3) The initiation of antimicrobial prophylaxis with AP significantly prolonged life in a group of patients with relatively advanced disease. This group was at a stage at which antiviral therapy with AZT may well be ineffective.

These points - that antimicrobial prophylaxis can in at least one circumstance prolong life, that it can do so in addition to whatever effect AZT may have had, and that it can do so in a circumstance where AZT may not be effective - are the empiric basis of our current therapeutic and investigational approach to AIDS. Until the next "cure" for AIDS comes along, we need to explore the limits of preventive medicine in this disease. If the onset of PCP can be delayed, it may also be possible to delay the onset of fungal, mycobacterial, and perhaps even viral infections in HIV-infected patients. While this approach is most emphatically palliative rather than curative, it is one that is probably within our reach over the next 2 to 3 years; and by that time, it is not unreasonable to hope that basic research will have identified and developed new approaches to control the underlying pathophysiology of this disease.

Figure 7

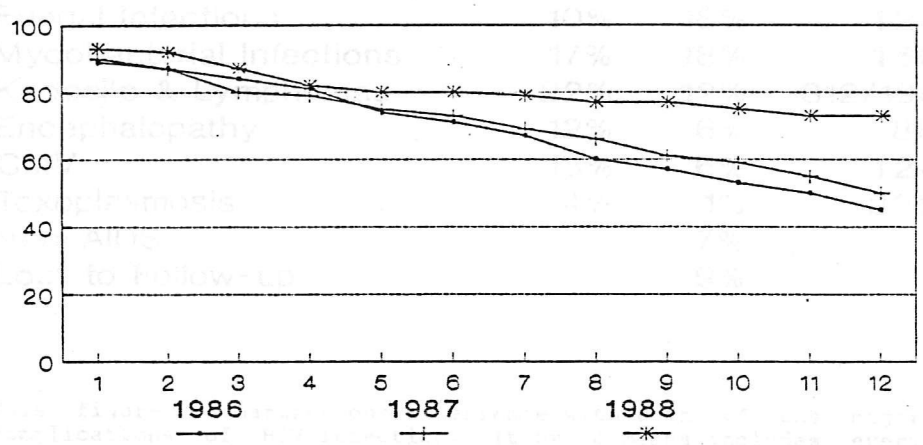
SURVIVAL AFTER AIDS DIAGNOSIS ALL PMH PATIENTS



The following discussion will describe the results of our therapy of the 752 patients with AIDS that had been treated at Parkland as of December 31, 1988. This figure shows the actuarial survival of these patients from the date of their AIDS diagnosis. Survival at one year was 47%, at 2 years 20%, and at 3 years 10%. These statistics are virtually identical to the San Francisco (6) and New York (7) experiences. At the top of the curve, 2% of our patients have died on the day AIDS was diagnosed, and 16% have died within 30 days of AIDS diagnosis. Subsequent mortality has been relatively linear at about 3% per month thereafter.

Figure 8

12 MONTH AIDS SURVIVAL
By Year Patient Entered PMH AIDS Clinic



Our more recent experience, however, appears to be improving. This figure illustrates the actuarial survival from AIDS diagnosis for the cohorts of patients who were first seen in our Clinic in 1986, 1987, and 1988. In 1986, the one year survival was 45%. In 1987, the one year survival was 50%. The projected one year survival in 1988, based on a mean follow-up of 6 months, is presently 73%. There is no difference in survival at 4 months among any of the cohorts, but the survival of the 1988 cohort appears to be better after this point. The overall 1988 survival is not yet significantly better than 1987 (the p on December 31 was only <.25), but the trend is clearly encouraging. Because of the survival data with AZT and AP therapy presented earlier, we believe that it is now reasonable, when counseling patients, to advise them that they now have about a 70%, rather than a 50%, chance of surviving at least one year after the diagnosis of AIDS.

Figure 9

AIDS AT PMH

	Incidence	Cause of Death	Mean Survival
Pneumocystis	70%	24%	395
Fungal Infections	10%	18%	125
Mycobacterial Infections	17%	18%	156
Kaposi's & Lymphomas	22%	12%	312/195
Encephalopathy	12%	6%	88
CMV	13%	6%	124
Toxoplasmosis	4%	1%	288
Non-AIDS		7%	
Lost to Follow-up		9%	

This figure summarizes our experience with each of the major complications of HIV infection. It by no means includes every complication we have seen, but it includes all those that were fatal between July 1 and December 31, 1988.

As of December 31, 1988, 65% of our patients had had PCP at the time of AIDS diagnosis, and another 5% had developed PCP at some time thereafter. Between July 1 and December 31, 1988, 22 of the 91 deaths in our AIDS patients have been due to PCP; 20 of these 22 deaths were in patients experiencing their first episode of PCP. The mean actuarial survival of all patients after their first episode of PCP was 395 days.

Cryptococcosis occurred in 6% of our patients, and histoplasmosis in 4%. The figure for cryptococcosis is identical to the national experience (8), and the figure for histoplasmosis reflects our geographic location in an area where histoplasmosis is endemic. While these fungal infections are, even collectively, relatively uncommon, they account for a disproportionate number of our deaths in the past 6 months; the mean actuarial survival after diagnosis of these infections is only 125 days.

Mycobacterium avium intracellulare (MAI) has been cultured from 14% of our patients, and M. tuberculosis (MTB), M. kansasii (MKA), or M. gordonae from another 3%. Mean survival after MAI has been only 156 days, while mean survival after disseminated MTB has been 368 days. One explanation for this difference is

that MTB is much more sensitive to available antimycobacterials than MAI. In our limited (4 cases) experience with MKA, it has clinically resembled MTB more than MAI in our patients. We have isolated M. gordonae from a few terminally ill patients who were infected with several other pathogens, but it does not appear that M. gordonae was anything other than a saprophyte in these cases. The other mycobacteria, however, are tied with fungal infections as the second most common cause of our deaths.

We have found Kaposi's sarcoma in 18% of our patients, and some other AIDS-related malignancy in another 4%. Survival after Kaposi's has not been as good in our experience as others have reported, and in our recent experience Kaposi's is that it is as much a tumor one dies "of" as it is a tumor one dies "with". Lymphomas are uniformly tumors that AIDS patients die "of".

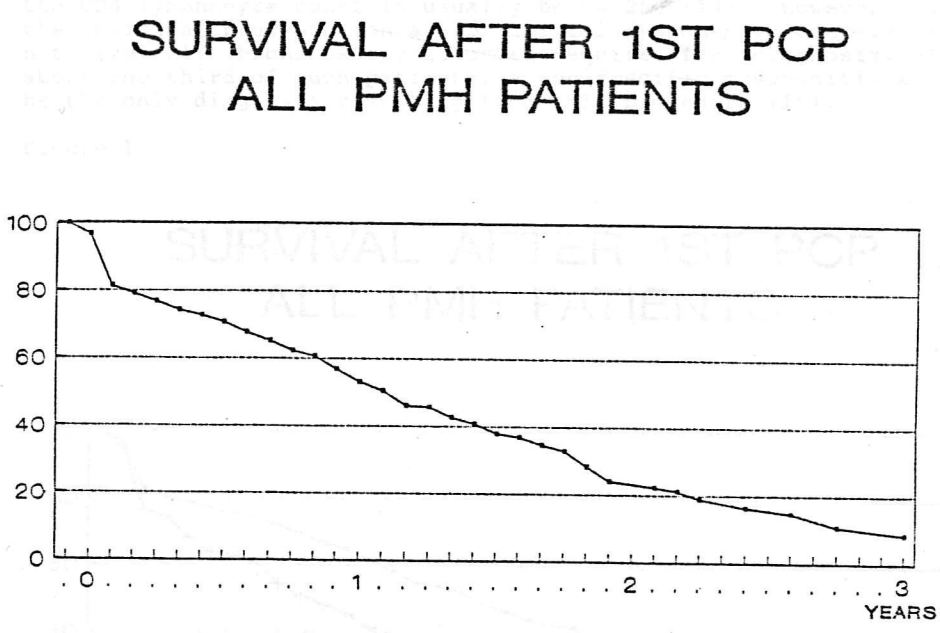
One eighth of our AIDS patients develop unequivocal and disabling loss of cognitive function that can be attributed to no cause other than primary HIV infection, and their mean survival after this complication has been diagnosed is the poorest of the lot.

Thirteen per cent of our patients have developed organ dysfunction as a result of documented CMV infection, and 6% of our patients in the past 6 months have died of this infection. Survival after documented CMV complications is also poor.

Toxoplasmosis occurs less frequently here, and has been rare as a primary cause of death in the past 6 months. Our experience with toxoplasmosis has so far been limited, but the results of this limited experience have been more favorable than we had expected.

Miscellaneous non-AIDS causes of death in the past 6 months were fulminant hepatitis in 2, suicide in 2, motor vehicle accident in 1, and acute myocardial infarction in 1. Finally, 9 patients who had not been seen here in over 6 months were found to have died elsewhere during this interval; we do not know the causes of their deaths.

Figure 10

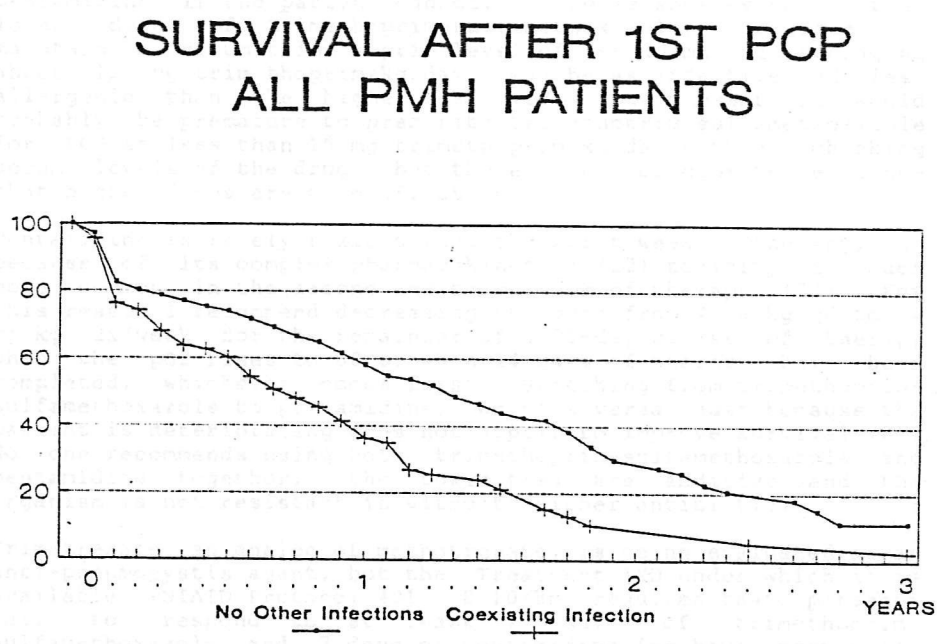


Our overall 30-day mortality for first PCP episodes has been 18%; it was 22% between July 1 and December 31, 1988. This is comparable to the experience of most other centers (9). The single most important prognostic factor appears to be the alveolar-arterial (Aa) oxygen gradient, and this in turn appears to be a function of how long the patient waits before seeking medical assistance. Mortality in one series (10 was 43% when the Aa gradient was > 30, 25% when the Aa gradient was 25-30, and 9% when the Aa gradient was < 25. The pO2 usually declines during the first few days of therapy, so we admit patients with a pO2 less than 60 for supplemental O2 and supervision of antibiotic therapy; compliance is a substantial problem when the pO2 is 45.

Most of our patients with PCP have presented with the characteristic clinical and radiographic features of the disease, but there have been enough exceptions to warrant the following comments. The classical radiographic picture in a typical clinical setting is usually diagnostic of the disease; but PCP can present with a granulomatous radiographic appearance suggestive of tuberculosis (11). Recurrent PCP in a patient on AP can present with a bilateral upper, rather than lower, lobe

reticulonodular infiltrate (12), because the aerosol is preferentially deposited in the lower lobes. Serum LDH is more likely to be elevated in PCP than in non-PCP pneumonias (13), and the CD4 lymphocyte count is usually below 250 (14). However, if the clinical presentation and/or initial response to therapy is not typical, bronchoscopy is often required for diagnosis. In about one third of such patients, a non-specific pneumonitis will be the only diagnosis resulting from this procedure (15).

Figure 11



About 20% of our 1st PCP cases have had one or more coincident AIDS complications. Suprisingly, the 30-day mortality of these 20% has not been significantly worse than for those who only had PCP, although their long-term prognosis is less favorable.

Trimethoprim-sulfamethoxazole (15-20 mg/kg of the trimethoprim component qd iv or po in 4 divided doses), trimethoprim-dapsone (same dose of trimethoprim, dapsone 100 mg qd po), and pentamidine (4mg/kg iv over 2 hours, checking blood glucose at 0, 30, and 120 minutes) appear to be equally effective in equivalent patients (16-18). Dapsone alone is not satisfactory (19). Because pneumocystis can be isolated from the lungs of many patients

after 14 days of therapy, because most patients have not completely recovered clinically after 14 days, and because the mortality of recurrent PCP is so high, current practice is to treat PCP for 21 days, regardless of the agent chosen.

Most of our HIV-positive patients appear to have some humoral immunity to sulfamethoxazole (20), and about half of the patients treated with trimethoprim-sulfamethoxazole develop a skin rash by the 7th day of therapy (21). Because the drug eruption can be severe, and because the allergy appears to be to sulfamethoxazole rather than to trimethoprim, we generally switch to trimethoprim-dapsone if the patient can tolerate oral therapy or to pentamidine if the patient cannot. There is some evidence that lower doses of trimethoprim-sulfamethoxazole, adjusted to maintain a serum trimethoprim level of 5-8 ug/mL and averaging about 12 mg trimethoprim/kg/day, may be as effective and less allergenic than the higher dose (17). At present it would probably be premature to prescribe trimethoprim-sulfamethoxazole for PCP at less than 15 mg trimethoprim/kg/day without checking serum levels of the drug, but there is no conclusive evidence that higher doses are more effective.

Pentamidine is rarely toxic during the first week of therapy, but because of its complex pharmacokinetics (22) toxicity is much more common in the second and third week of therapy (23). For this reason I recommend decreasing the dose from 4 mg/kg qd to 4 mg/kg 2x/week for the remainder of a 21-day course of therapy when the pO2 rises to 60 or when 14 days of therapy have been completed, whichever comes first. Switching from trimethoprim-sulfamethoxazole to pentamidine, or vice versa, just because the patient is deteriorating does not appear to improve survival (8). No one recommends using both trimethoprim-sulfamethoxazole and pentamidine together; the toxicities are additive and the organism is not resistant in vitro to either antibiotic.

Trimetrexate, an analog of methotrexate, is being evaluated as an anti-pneumocystis agent, but the Treatment IND under which it is available (NIAID Protocol 401, 8/10/88) requires that patients fail to respond to at least 7 days of trimethoprim-sulfamethoxazole and 7 days of pentamidine (or have previously had a life-threatening reaction to one or both drugs). Results with trimetrexate so far appear comparable, but not clearly superior, to results with trimethoprim-sulfamethoxazole or pentamidine (24).

Adjunctive steroid therapy for PCP (25) has been very popular at Parkland recently. Virtually all of our first PCP patients who died between July 1 and December 31, 1988 received steroids, usually solumedrol 60 mg q6h iv x 5-7 days, as did many who survived. However, as noted above, our mortality during this period was no better than before this practice began, so there is no evidence from our uncontrolled experience that adjunctive steroid therapy has been beneficial.

Aerosolized pentamidine (AP) has been proposed as a primary treatment for "mild" PCP (26), but it has not yet been shown to be more effective than, say, trimethoprim-dapsone, and it is much more expensive. I do not recommend AP as a sole therapy for PCP at this time. It remains to be demonstrated that the aerosolized drug can penetrate the infected portions of the lung, and AP can cause a severe cough which, in a hypoxic patient, could be life-threatening. I do, however, recommend beginning AP prophylaxis against recurrence of PCP as soon as the patient has recovered from the acute episode.

The short-term prognosis of patients with PCP who require mechanical ventilation is reported to be about 14% (27); for those who receive cardiopulmonary resuscitation, it is reported to be about 2% (28). Patients who must decide whether or not to request intubation in the event of respiratory failure may not be aware of this data. In a survey at San Francisco General Hospital, the mean estimate given by 118 patients of survival after intubation for first PCP was 53% (29). Interestingly, these patients' personal preferences for or against intubation were not correlated with their estimates of survival, whereas physicians' own preferences for or against intubation of patients have been correlated with their estimates of the patients' chance of survival (30). However, physicians' preferences for or against intubation, in the same circumstance as reference 29, have also been correlated with their highly idiosyncratic attitudes toward risk (31), so it is possible that patients' decisions regarding intubation may be influenced by equally non-rational psychological processes.

Telling young men they are probably going to die is an unpleasant task; accepting the fact that one's own best efforts to prevent this event are probably going to be inadequate is an equally unpleasant one. When the time for this task comes, I usually begin the discussion with the phrase, "Mr. _____, I have to tell you some things." Those are that, depending on the circumstances, "1 (to 9) out of 10 people I treat for this condition survive, but 9 (to 1) do not. If your lungs fail, we may be able to keep you alive for a few days on a respirator while we keep treating your pneumonia. There is about 1 chance in 10 this will prolong your life, but about 9 chances in 10 this will prolong your death. Whatever you decide about the respirator, we will do everything we can to make you better and make you comfortable." The responses I get are about equally divided between "no respirator" and "let we think about it", but one usually gets an informed decision within 24 hours.

The best way to treat PCP is to prevent it. AZT, as noted above (1), delays the onset of PCP, at least in others' hands. Trimethoprim-sulfamethoxazole, one double-strength (160 mg trimethoprim) tablet twice a day, is also an effective prophylaxis (32), but only half the patients started on it can tolerate it for 90 days. Fansidar has been used for PCP prophylaxis, but a fatal reaction to it has been reported (33). For these reasons, we have largely relied on aerosolized

pentamidine (AP) for prophlyaxis against PCP. Between July 1 and December 31 we treated 99 patients with ARC or a CD4 count < 400 with AP 300 mg/mo in an open, uncontrolled trial. The mean duration of treatment was 113 days. During this time we identified only one possible instance of PCP in these 99 patients.

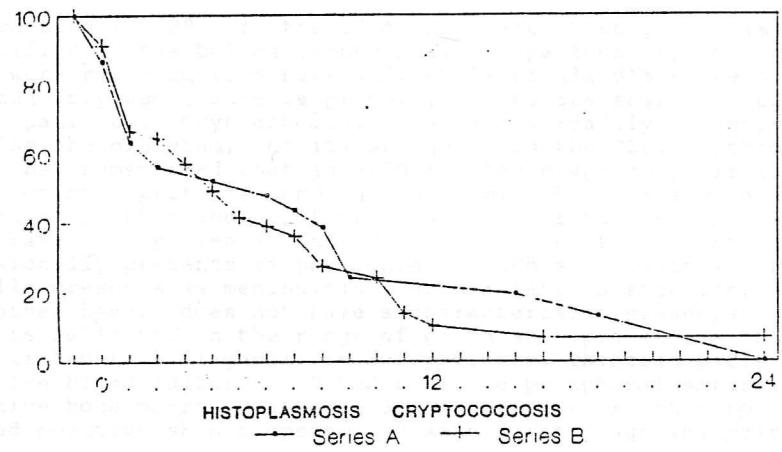
Prevention is even more important for patients who have had PCP before. Relapse rates are about 35% at 6 months for patients not on AZT, and about 19% for patients on AZT (9). Mortality of recurrent PCP is about 40% per episode; it was 45% (5/11) at Parkland between July 1 and December 31, 1988. We have treated 153 patients with a prior episode of PCP with AP, 300 mg q month, for a mean of 121 days; 11 (7%) relapsed during this time. All these patients were offered AZT, and almost all were taking it. The patients who relapsed had had their first episode of PCP at least 282 days (median 439) before they had their first AP treatment.

Because of this experience, we plan to initiate a randomized comparison of 300 mg vs 600 mg AP per month for prophylaxis of patients who survived more than one year after their first PCP episode. Since the patients absorb only about 5% of the administered dose (34) the high dose will probably not be toxic, but there is a possibility that it will. We have found a small but highly significant decrease in FEF25-75, from 113% to 91% of predicted, in 24 patients who had pulmonary function tests before and 6 months after beginning therapy, and this observation needs to be followed up. We have also diagnosed bacterial pneumonia in 4 of the 308 patients that have received AP therapy after a mean follow-up of only 120 days. Also, 2/14 patients on AP who developed PCP had pneumothoraces, compared to 2 pneumothoraces in 93 first PCP patients between July 1 and December 31, 1988 who had not received AP ($p<.05$). Overall, AP has been a very effective therapy for our patients, but its long-term side effects remain uncertain, and it must continue to be used with caution.

Finally, we have diagnosed only 2 cases of extrapulmonary pneumocystis infection so far, but this complication is being reported with increasing frequency (35).

Figure 12

SURVIVAL IN AIDS-RELATED HISTOPLASMOSIS & CRYPTOCOCCOSIS



Most of the opportunistic infections of AIDS have slow, indolent courses; cryptococcosis and histoplasmosis do not. In retrospect, the patients often have had about a month's history of increasing fevers, fatigue, weight loss, and headache, but except for the last these are nonspecific and of no useful predictive value for the diagnosis. The chronic prodrome becomes a fulminant illness that most closely resembles bacterial septicemia in a day or so, and it is rapidly fatal unless diagnosed and treated immediately. One-third of our patients with cryptococcosis and histoplasmosis have died within 30 days of the procedure that established the diagnosis; but at least in the case of histoplasmosis, all of those in whom the disease was recognized early enough so that at least 100 mg amphotericin B could be administered have survived long enough to receive a full course of amphotericin B therapy. This is the explanation for the flattening of the survival curves during the second and third month after the diagnosis. However, cures of AIDS-related cryptococcosis and histoplasmosis are very uncommon; less than 5% of our patients have been cured. For the remainder, suppressive therapy with amphotericin B is necessary, and despite this suppressive therapy relapses are common, as suggested by the progressive decline in survival after 120 days.

At this point we can briefly stabilize the patient by resuming daily amphotericin B therapy, but death usually occurs within weeks after the fungus breaks through the suppressive therapy.

Cryptococcosis occurs in about 6% of AIDS patients nationwide, and has occurred in 6% of our own. There is no geographic variation in its incidence. Histoplasmosis, on the other hand, is rare in AIDS patients who do not reside in states (such as Texas) where histoplasmosis is endemic (7). Histoplasmosis was diagnosed in 5% of all AIDS cases in the Houston area (36); its incidence is about 4% of all AIDS cases at Parkland.

Interestingly, 29 of the 32 AIDS-related histoplasmosis cases identified by the Dallas County Health Department by December 16, 1988 were reported from Parkland, while Parkland's share of AIDS-related cryptococcosis is proportional to its share of Dallas's AIDS patients. Cryptococcosis is fairly readily diagnosed by finding the organism, or its antigen, in the CSF, although it must be remembered that in AIDS-related cryptococcosis the CSF cell count, protein, and glucose may be normal, and that meningismus, photophobia, focal neurologic findings, and seizures are rare at presentation (37). AIDS-related cryptococcosis occasionally presents as pneumonia or with skin lesions, but it usually presents as meningitis. AIDS-related histoplasmosis, on the other hand, does not have a characteristic presentation, and this is reflected in the range of diagnostic procedures that have established this diagnosis in our patients. Thirteen patients had positive blood cultures, 9 had positive peripheral smears, 7 had positive bone marrow cultures, 3 had positive bronchoscopies, and 2 had positive skin biopsies; 3 were first diagnosed postmortem (38).

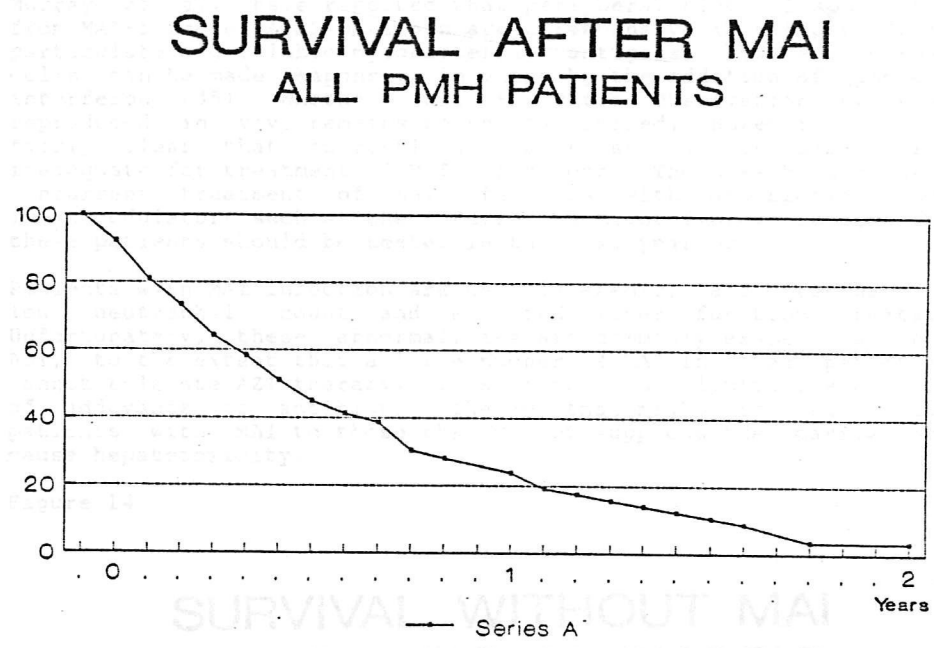
Treatment of AIDS-related cryptococcosis and histoplasmosis with amphotericin B is palliative and toxic; the addition of flucytosine to amphotericin B increases the toxicity without increasing the efficacy of therapy; and ketoconazole is ineffective, at least in our hands, either as a prophylactic or a suppressive therapy (38). Since we do not expect to cure these infections, the dose of amphotericin B we prescribe in an individual case is the minimum amount we believe necessary to suppress the infection rather than the maximum amount we believe the patient can tolerate.

Fortunately, there is a new agent, fluconazole, which appears to be substantially more effective than amphotericin and substantially less toxic (39-41). Fluconazole can be given either orally or intravenously. Because it can be taken orally, it could possibly be used as a prophylaxis against cryptococcosis and histoplasmosis as well as for treatment of these conditions. Since oral fluconazole is also an effective treatment for mucosal candidiasis, we anticipate that a large majority of our patients will receive fluconazole as soon as it is released by the FDA. We are cautiously optimistic that this will happen soon, and cautiously optimistic that fluconazole and/or its congeners such as itraconazole will have a substantial beneficial impact on

survival of AIDS patients with systemic fungal infections.

Until these new drugs become available, our only hope of improving survival in AIDS-related cryptococccosis and histoplasmosis will be earlier diagnosis. We have recently initiated the practice of screening our Clinic patients with ARC and/or a CD4 count < 400 for asymptomatic fungemia with monthly isolator tube blood cultures. We screen this population because cryptococcosis was the first opportunistic infection (other than oral thrush) to occur in 32 (68%) of our 47 patients with this infection, and histoplasmosis was the first opportunistic infection (other than oral thrush) to occur in 26 (87%) of our 30 patients with this infection (38). If screening for fungal infections is going to be effective, it will have to include patients who have not yet been diagnosed as having AIDS. In the limited time since we began this routine surveillance we have diagnosed one case of cryptococcosis, who died despite therapy, and one case of histoplasmosis, who completed a 1500 mg course of amphotericin and is now stable off all antifungal therapy. We hope to know if this strategy is effective, and in whom it is cost-effective, by the end of this calendar year.

Figure 13



When I first started working in the Parkland AIDS Clinic last February, it seemed as if almost all the patients had low grade fevers, slow but persistent weight loss, anemia, abdominal pain, and chronic diarrhea. With the widespread application of AZT and AP, it has been most gratifying to see these symptoms abate in the large majority of patients, although they did not abate in all. Those in whom they did not abate have almost invariably proven to have mycobacterium avium intracellulare (MAI) bacteremia. MAI is now readily identifiable as the principal cause of "wasting syndrome" in our AIDS patients.

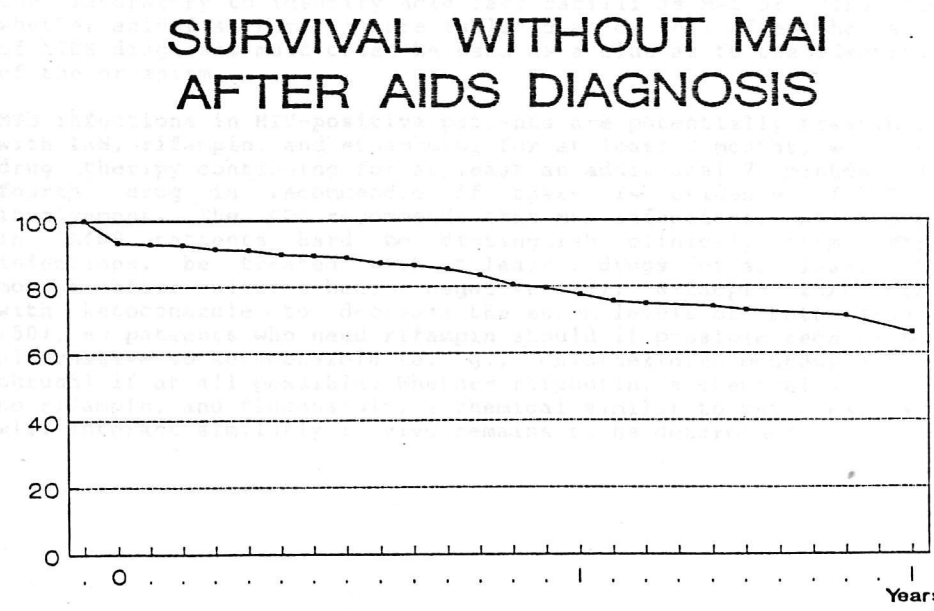
Survival after the diagnosis of MAI infection is about 5 months. MAI is generally resistant in vitro to conventional antituberculosis medications; for example, only 6% of MAI strains tested by one laboratory were sensitive to rifampin (42). MAI is variably sensitive in vitro to rifabutin (also known as ansamycin), clofazamine, ethambutol, amikacin, imipenem, and ciprofloxacin, but in vivo even combinations of these antibiotics rarely if ever eradicate MAI infection (43-44). Because our own experience has been no more favorable than that reported in the literature, we do not generally attempt to treat established MAI

infection with these antibiotics. The one exception to this might be those few who present with MAI but no other opportunistic infection.

Murray et al. have reported that peripheral blood lymphocytes from MAI-infected AIDS patients are unresponsive in vitro to both particulate and soluble mycobacterial antigens; however, these cells can be made responsive in vitro by the addition of gamma-interferon (45). Whether this in vitro observation can be reproduced in vivo remains to be determined. However, it is fairly clear that currently available antibiotics alone are inadequate for treatment of MAI infections. The possibility that concurrent treatment of MAI infections with antibiotics and immunomodulators such as the interferons might improve outcome in these patients should be tested in the next year or so.

Patients with MAI infection are usually anemic, and often have a low neutrophil count and elevated liver function tests. Unfortunately, these abnormalities are commonly exacerbated by AZT, to the extent that a large number of MAI-infected patients cannot tolerate AZT therapy. This circumstance limits the choice of adjuvants to antibiotic therapy that might be tested in patients with MAI to those that do not suppress the marrow or cause hepatotoxicity.

Figure 14

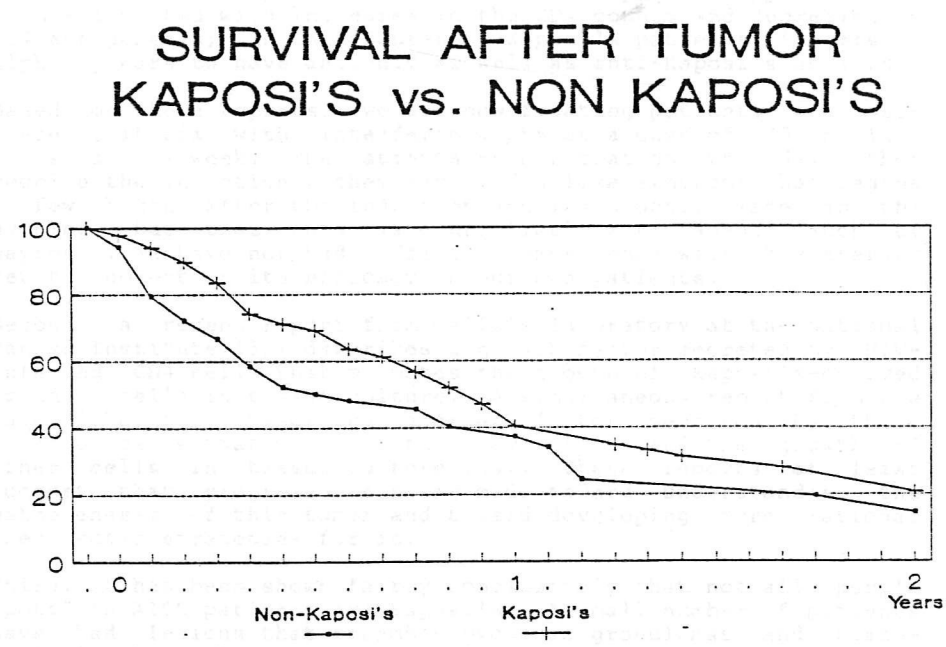


About 7% of our patients have had documented MAI infection at the time of AIDS diagnosis. After this time, new MAI infections occur at a very constant rate of 1% per month. At this rate, it would be cost-effective to attempt prophylaxis against MAI infection in AIDS patients if a suitable agent were available. A trial of clofazamine prophylaxis against MAI is currently in progress in San Francisco, and we are presently negotiating with the manufacturer of rifabutin to implement a randomized, blinded, placebo-controlled trial of this agent as a prophylaxis against MAI. To perform a study that would have an 80% chance of detecting a decrement in MAI infection rate from 10% to 2.5% in one year (in one study, 81% of MAI isolates were sensitive to rifabutin in vitro (42)), we would need 162 patients in the treatment arm and 162 patients in the control arm (46). This would require the participation of almost all the active AIDS patients in our Clinic. Since the FDA does not, for good reason, permit patients to be enrolled in more than one experimental drug trial at the same time, this study would become the major research enterprise of the Clinic for the next 12 months.

A small percentage of HIV-positive patients develop disseminated M. tuberculosis (MTB) or M. kansasii (MKA) infections. Pulmonary MTB alone is not a criterion for AIDS; in HIV-positive patients, pulmonary MTB usually develops in the 6 months before the patient acquires another infection that establishes the diagnosis of AIDS (47). Disseminated MTB, which is a criterion for AIDS, is usually diagnosed as or with the first opportunistic infection that establishes the AIDS diagnosis (48). It takes several weeks for the laboratory to identify acid-fast bacilli as MAI or MTB, so whether acid-fast bacilli are isolated at or well after the date of AIDS diagnosis must often be used as a clue as to the identity of the organism.

MTB infections in HIV-positive patients are potentially treatable with INH, rifampin, and ethambutol for at least 2 months, with 2-drug therapy continuing for at least an additional 7 months. A fourth drug is recommended if there is evidence of CNS involvement. The CDC recommends that MKA infections, which are in AIDS patients hard to distinguish clinicaly from MTB infections, be treated with at least 2 drugs for at least 15 months after cultures become negative (49). Rifampin interacts with ketoconazole to decrease the serum levels of both drugs (50), so patients who need rifampin should if possible receive an alternative to ketoconazole (e. g., chlorhexidine mouthwash for thrush) if at all possible. Whether rifabutin, a chemical similar to rifampin, and fluconazole, a chemical similar to ketoconazole, will interact similarly in vivo remains to be determined.

Figure 15



Kaposi's sarcoma has occurred in 18% of our AIDS patients. Its incidence nationwide has declined from 31% to 14% (8). At Parkland 22% of our patients through 1986 had Kaposi's, while 16% of our 1987-88 patients have had it. Kaposi's is, like PCP, fungal, and MTB infections, a "sentinel" manifestation of AIDS; in 77% of our patients Kaposi's was present at the time AIDS was diagnosed. We have not found Kaposi's to be significantly more common in patients who have a history of intravenous drug use, or in one particular racial group. Nationally, patients with Kaposi's have had a somewhat better survival than other AIDS patients, but that has not been the case here. Our experience with Kaposi's probably just reflects lead-time bias (patients get here late, so their Kaposi's is documented late), but we do not have sufficient data to confirm this impression.

Three promising developments have recently occurred in the area of Kaposi's. First, recombinant interferon alpha has recently been released for treatment of Kaposi's sarcoma. The available evidence to date strongly suggests that interferon alpha is most effective in patients with Kaposi's who have a CD4 count above 200 and who have not had other opportunistic infections such as

PCP; in such patients, partial response rates up to 50% have been reported (51). In patients with the higher CD4 counts, Lane et al. (52) have reported that interferon alpha therapy has also been associated with increases in the CD4 counts and decreases in p24 antigenemia; in this subset of Kaposi's patients, interferon alpha appears to have anti-HIV as well as anti-Kaposi's activity.

Based on these reports, we are now treating patients who meet these criteria with interferon alpha at a dose of 30 million units sc 3x/week. The patients report that on the days they receive the injections, they have a flu-like syndrome that begins a few hours after the injection and lasts until late in the evening, but that this is controllable with agents such as naprosyn. We have not had sufficient experience with this therapy yet to comment on its efficacy in our own patients.

Second, a recent report from Gallo's laboratory at the National Cancer Institute (53) describes a growth factor secreted by HIV-infected CD4 cells that promotes the growth of Kaposi's-derived spindle cells in tissue culture. A simultaneous report from the same laboratory describes a growth factor secreted by these spindle cells that promotes their own growth and the growth of other cells in tissue culture (54). These reports at least suggest that progress is being made toward understanding the pathogenesis of this tumor and toward developing more rational therapeutic strategies for it.

Third, it has been shown fairly conclusively that not all "purple spots" on AIDS patients are Kaposi's. A small number of patients have had lesions that resemble pyogenic granulomas and histologically have the appearance of "epithelioid angiomatosis". With appropriate staining techniques, bacteria have been demonstrated in these lesions that have the characteristics of the cat-scratch bacillus, and a few patients have responded to erythromycin therapy (55-56).

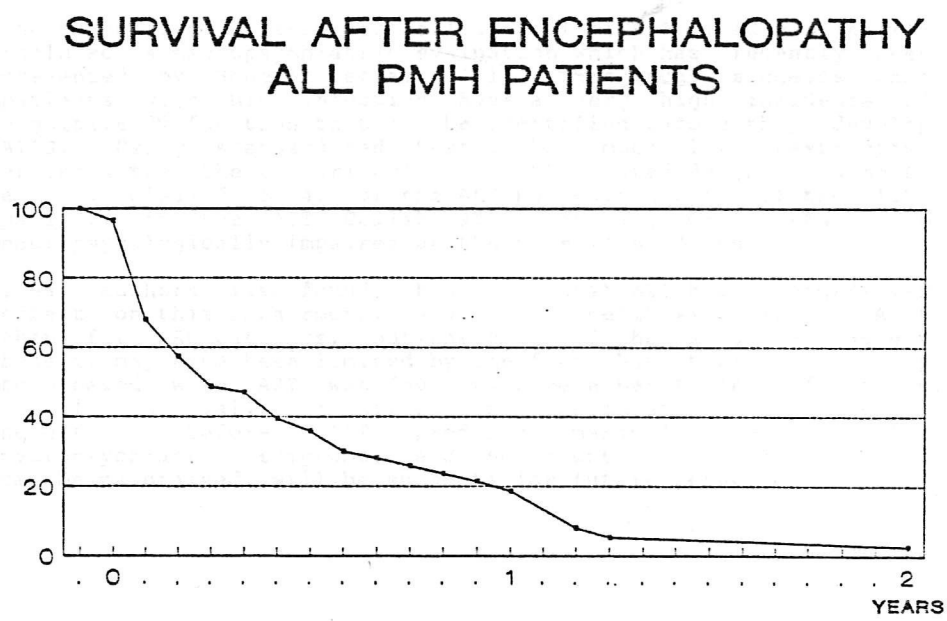
For patients with superficial lesions, we have had excellent results with palliative radiotherapy. Radiotherapy does not make the lesions disappear completely; but it has reduced their size and the symptoms associated with them, and it has done so with minimal toxicity. Chemotherapy of Kaposi's in our hands for visceral Kaposi's has not generally been effective and has been associated with considerable hematological toxicity. Others have found that chemotherapy of Kaposi's is no less toxic when it is combined with interferon, so this combination is not recommended (57). This unfavorable experience with chemotherapy is one reason why we are so actively pursuing interferon alpha treatment in the early stages of Kaposi's.

Non-Hodgkin lymphoma, Hodgkin disease, and perhaps other solid and hematologic tumors occur in a small but discernable number of AIDS patients. Our median survival rate for these patients is 5 months, the same as others have reported (58). Most of the patients with these malignancies at Parkland have had coexisting infections which precluded aggressive chemotherapy. This reflects

a general characteristic of Parkland's AIDS population; over half of our AIDS patients have had the diagnosis of AIDS established at or before the time they first present to us. However, centers where patients present at earlier stages of HIV infection have reported that about 1/3 of their lymphoma patients are diagnosed before other opportunistic infections have developed, and in this subset chemotherapy may be a viable option. The Pacific Presbyterian Medical Center in San Francisco has recently reported an overall 52% response rate to chemotherapy for AIDS-related lymphomas, and a 64% complete response rate for patients who were judged able to tolerate a MACOP-B regimen. The median survival of those who achieved a complete remission was 20 months (59).

It is possible that, as AZT and antimicrobial prophylaxis regimens prolong both survival and disease-free survival of HIV-infected patients, more cases of AIDS-related malignancies will be seen, and seen before other opportunistic infections have occurred. If this happens, the experience cited above suggests that chemotherapy may come to play a larger role in the care of AIDS patients than it does at present.

Figure 16



The most common neurologic complication of HIV infection is a loss of memory and an inability to concentrate that in some cases rapidly progresses to global dementia. The cognitive dysfunction is often accompanied or followed by motor dysfunction that can progress to quadriparesis (60). We have found this condition, and found no infectious, metabolic, or neoplastic cause other than HIV infection, in one out of every 8 AIDS patients in the Parkland experience.

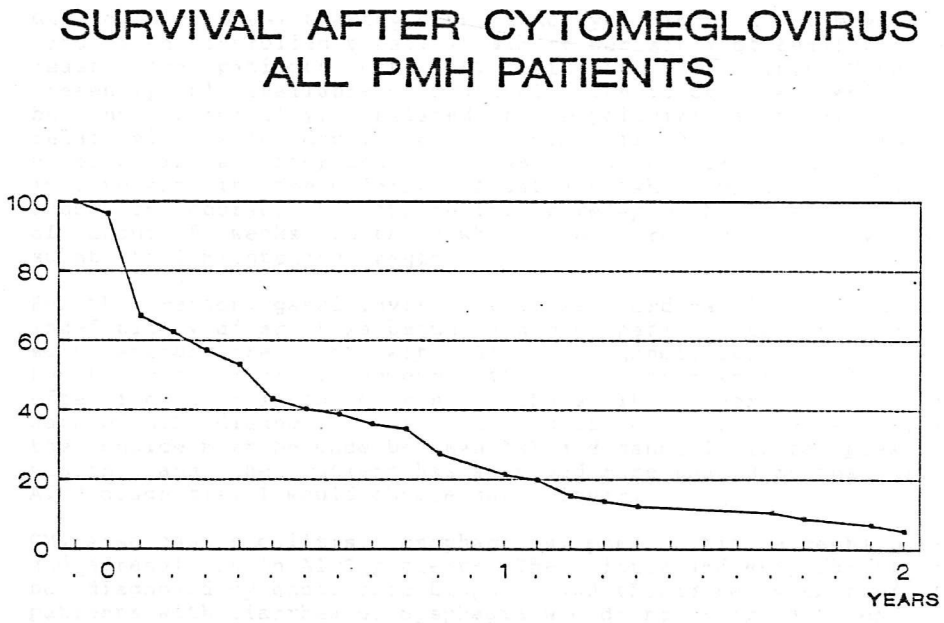
These were "clinical" diagnoses. However, for such a diagnosis to be entered into our registry, the patient had to meet the CDC criteria for AIDS dementia to the satisfaction of an independent reviewer; these criteria include adequate chart documentation of cognitive impairment and laboratory investigation, including a CT scan and examination of the CSF, that excluded other causes of cognitive impairment. These patients were severly ill; mean survival after the diagnosis of AIDS dementia in our patients has been only 88 days. In fact, the diagnosis of AIDS dementia is quite obvious, and if anything we have been too conservative rather than too liberal in making this diagnosis. Some of our patients with AIDS dementia have responded dramatically to AZT

therapy; however, while we have seen an occasional patient with severe dementia who returned to a satisfactory level of cognitive function, the majority of the severely impaired have not.

The randomized, placebo-controlled trial of AZT cited earlier (1) included a neuropsychiatric evaluation which has recently been presented by Schmitt et al. (61). This study suggests that patients with HIV infection have a very high incidence of cognitive dysfunction that can be identified before they develop AIDS. Using standardized tests, but much less restrictive criteria than the CDC criteria for AIDS-related dementia, Schmitt et al. classified 41% of the ARC patients and 55% of the AIDS patients in the AZT Collaborative Working Group study as neuropsycologically impaired at the time of study entry.

These authors also found, however, that AZT had a beneficial effect on this impairment. A greater benefit was seen for AIDS than for ARC patients, but the power of the study to detect benefit may have been limited by the fact that it was prematurely terminated when AZT was found to have a beneficial effect on overall survival. For this reason, the duration of treatment necessary before AZT produces maximal benefit for neuropsychiatric symptoms, and the amount of time this benefit can be maintained, will be subjects for future research.

Figure 17



Cytomegalovirus (CMV), like MAI, is characteristically a late complication of AIDS, and these two have now become the most common complications seen in our long-term survivors. The incidence of CMV retinitis varies from one center to another, but this variation probably reflects the proportion of long-term survivors in a center's patient population. CMV retinitis presents as a painless and at first modest loss of visual acuity, blurred vision, or blind spots. When symptoms first occur, the retinal lesions may be in the periphery of the retina and missed by routine ophthalmoscopy, so referral for a complete ophthalmologic examination is necessary to establish the diagnosis. In the later stages of CMV retinitis, the florid picture of "catsup on cottage cheese" all over the retina is easy to observe (62-63).

The focus of the initial ophthalmologic examination should be on whether any retinal lesions observed are hemorrhagic or exudative. Cotton wool spots around blood vessels are seen with some frequency in AIDS patients and are apparently benign; cotton wool spots do not contain hemorrhage or exudate. For those that do, the differential diagnosis in an AIDS patient includes

toxoplasmosis, candida emboli, syphilis, and herpes simplex. These can only be excluded indirectly, by finding no evidence of these conditions elsewhere and by identifying active CMV infection in other organs by culture or biopsy (64).

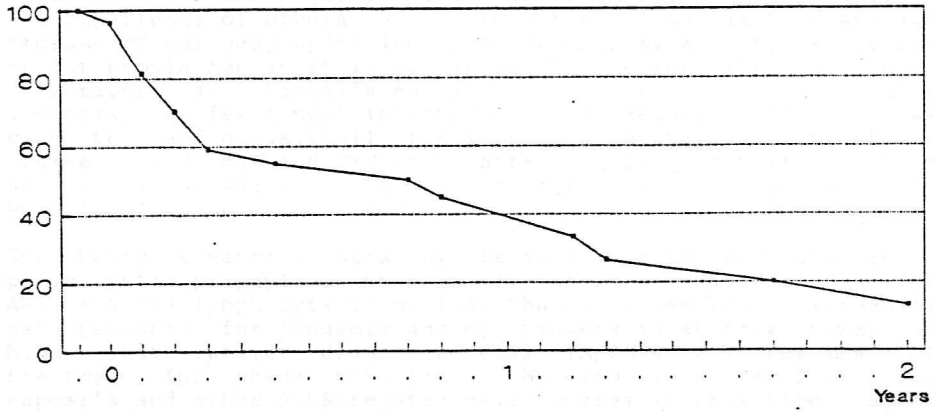
Ganciclovir (DHPG) therapy, while not yet rigorously tested in a randomized controlled trial, is almost certainly of benefit to at least some patients with CMV retinitis (65). This drug is presently only available on protocol. Ganciclovir is chemically, but not clinically, related to acyclovir; acyclovir is a relatively safe drug, but ganciclovir can cause severe neutropenia at therapeutic doses. Ganciclovir produces some improvement in the majority of patients who complete a 14-day induction course, but the retinitis relapses at a mean interval of about 6 weeks in those who do not receive a relatively substantial maintenance regimen.

For this reason, ganciclovir therapy will ordinarily be continued indefinitely after it is begun, and most patients cannot tolerate simultaneous treatment with AZT and ganciclovir because of hematologic toxicity. However, it is uncertain whether AZT is as effective late in the course of AIDS as it is shortly after the date of AIDS diagnosis, as mentioned above. For this reason, if the choice must be made between AZT and ganciclovir to preserve vision, and the patient has survived more than 9 months after AIDS diagnosis, I would choose ganciclovir.

CMV also causes colitis, esophagitis, pneumonitis, encephalitis, and adrenalitis in AIDS patients. The colitis and esophagitis can be diagnosed by endoscopic biopsy, and should be suspected in patients with diarrhea or dysphagia who do not respond to empiric trials of antibiotics or antivirals. CMV is rare (4%) as the sole cause of pneumonitis in AIDS patients, and how often it causes "AIDS dementia" is uncertain outside of autopsy series. In Dr. Dennis Burns' series of AIDS cases that were autopsied at our institution, CMV encephalitis was identified in 20%. Adrenal infection with CMV is a common autopsy finding, and we ar currently investigation the extent to which this finding can be correlated with antemortem signs or symptoms of adrenal insufficiency.

Figure 18

SURVIVAL AFTER TOXOPLASMOSIS
ALL PMH PATIENTS



The survival of our patients with toxoplasmosis has been better than one might expect, but comparable to the experience in France where toxoplasmosis is more common. AIDS-related toxoplasmosis is the first opportunistic infection in about half the patients in whom it occurs, and for this reason it probably arises by reactivation of a latent infection. However, about half the population of the United States has serologic evidence of prior exposure to toxoplasmosis, so why only a few AIDS patients develop it is presently uncertain (66).

Toxoplasmosis is the most common infectious cause of focal neurologic deficits in AIDS patients, and the demonstration of contrast-enhancing ring or nodular lesions on CT scan in AIDS patients with focal neurologic deficits and no other obvious (and treatable) cause for these defects is sufficient to warrant empiric therapy. Serology is useful only if negative; the presence of antitoxoplasma antibodies in serum is not diagnostic. It has been said that CSF antibodies to toxoplasmosis are diagnostic of cerebral involvement (67), but we are presently following 2 patients with these antibodies but without CT evidence of toxoplasmosis off treatment, and they have not (yet)

SUMMARY

There has been a pause in the AIDS epidemic at Parkland in the past year or so. While AZT and aerosolized pentamidine have been effective therapies, their institution does not completely explain this pause. Whether the future course of the epidemic at Parkland will be down, up, or way up remains to be seen. Everywhere else it is way up.

The overall survival of our AIDS patients, and their survival after onset of the major complications of AIDS, is comparable to the experience of others. We see more histoplasmosis than average because of our geographic location, and Kaposi's is not as benign in our population as it is elsewhere. We see PCP, systemic fungal infections, and Kaposi's early in our patients' courses, some dementia, a few fungal infections, less recurrent PCP than we used to, and occasionally toxoplasmosis in the midst of these courses, and MAI and CMV with increasing frequency in long-term survivors. We see a lot of other things, too, but they have not been fatal in our recent experience.

Our basic treatment strategy is to institute AZT and anti-pneumocystis prophylaxis when an HIV-infected individual develops ARC or a CD4 lymphocyte count less than 400. We begin screening our patients for fungemia and mycobacteremia at this time, in hope that earlier diagnosis will improve the results of treatment for these conditions. We also look carefully for Kaposi's and other AIDS-related malignancies at this time, again in the hope that interferon-alpha or, in selected cases, chemotherapy can be instituted at a time when it may be of benefit.

Our own research program is presently focused on evaluation of prophylactic measures to delay the onset of opportunistic infections in our patients, and social factors that influence our patients' acquisition of treatment. We are gratified by the early results of aerosolized pentamidine but closely monitoring this program to determine the incidence of its long-term side effects. We are attempting to develop research protocols to evaluate the effectiveness, and the cost-effectiveness, of prophylaxis with various antifungal and antimycobacterial agents, alone or in combination. At the same time, we would like to know why so many of our patients wait until the very last minute, and too often even later, before they present for treatment, and what we might be able to do to change this. If both arms of this research are productive, either here or at similar institutions pursuing similar objectives, there is a chance that the present 1 year 73% survival after AIDS diagnosis of our Clinic patients could improve a bit over the next year or two; and there is also a chance that by that time there may be an antiretroviral therapeutic advance that might improve patient survival even more.

ACKNOWLEDGEMENTS

The Parkland AIDS experience reported here was abstracted from the registry that was conceived, developed, and maintained by Mr. Jonathan Jockusch. Without his skill and dedication, and that of those who assisted him, this review would not have been possible.

Stephen D. Nightingale, M. D.
15 February 1989

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